Eur J Pediatr (1995) 154:700–707

ORIGINAL PAPER

Hans-Heiner Kramer
Michael Sommer
Spyros Rammos
Otto Krogmann

Evaluation of low dose prostaglandin E_1 treatment for ductus dependent congenital heart disease

Received: 20 January 1995
Accepted: 20 April 1995

H.-H. Kramer · M. Sommer · S. Rammos
O. Krogmann
Department of Paediatric Cardiology,
Children's Hospital,
Heinrich-Heine-University,
Düsseldorf, Germany

H.-H. Kramer (✉)
Clinic for Paediatric Cardiology,
Christian-Albrechts-University,
Schwanenweg 20,
D-24105 Kiel 1, Germany
Tel.: 49–431/5971728
Fax: 49–431/5971828

Abstract This study reports our experience with low-dose prostaglandin E_1 (PGE_1) treatment of 91 newborns with ductus dependent congenital heart disease (CHD). PGE_1 efficacy, side-effects as well as the cardiovascular and respiratory profile of the patients were analysed. PGE_1 doses > 0.02 μg/kg per minute were used for only 5.3% of the total 23656 h of treatment. The mean systolic blood pressures did not differ from the normal mean for patients with cyanotic CHD, while the diastolic values were lowered. Respiratory support was required only during 13.7% of the total treatment time. Apnoeas occurred in 21 (38%) of the 55 spontaneously breathing infants, who all had a cyanotic CHD. The incidence of apnoeas was lower during treatment with doses < 0.01 μg/kg per minute.

Conclusion PGE_1 can be successfully administered in lower doses than previously recommended. Especially high initial doses can be avoided and low maintenance doses allow long-term treatment without serious complications.

Key words Congenital heart disease · Prostaglandin E_1 · Efficacy · Side-effects · Cardiovascular and respiratory profile

Abbreviations *BAS* balloon atrial septostomy · *CHD* congenital heart disease · *PGE_1* prostaglandin E_1 · *SD* standard deviation · *SO_2* oxygen saturation

Introduction

Prostaglandin E_1 (PGE_1) therapy plays an important role in the pre-operative management of newborns with ductus dependent congenital heart disease (CHD). Unfortunately, however, side-effects (e.g. apnoea or systemic hypotension) are common, especially when doses as high as 0.1 μg/kg per minute are used [7], which have been recommended for initial treatment [5, 20]. After initial experience with complications obviously due to high PGE_1 dosages requiring intensive care, particularly artificial ventilation, we subsequently followed a low-dose regime to avoid side-effects. Although many paediatric cardiologists are now administering lower PGE_1 doses, experiences with a larger patient population have not recently been published. We, therefore, report our experience with low-dose PGE_1 infusion with regard to efficacy and side-effects with special emphasis on the analysis of the cardiovascular and respiratory profile of these patients.

Patients and methods

The charts of 91 newborns (58 males, 33 females) with ductus dependent CHD treated with intravenous PGE_1 infusions (Minprog Paed) between January 1986 and April 1992 were reviewed. The cardiac diagnoses are listed in Table 1. Of the 73 cases with cyanotic heart disease, 50 were classified as having complete transposition (group 1) and 23 as having ductus dependent pulmonary circulation (group 2). Eighteen newborns had ductus dependent

Table 1 Cardiac diagnoses

	n
Group 1	
Complete transposition	50
Group 2	
CHD with obstructed pulmonary blood flow	
Pulmonary atresia/critical pulmonary stenosis	6
Tricuspid atresia	5
Tetralogy of Fallot/pulmonary atresia with ventricular septal defect	7
Other complex cyanotic heart disease	5
Group 3	
CHD with restricted systemic blood flow	
Preductal coarctation	15
Interrupted aortic arch	1
Critical aortic stenosis	2

acyanotic heart disease (group 3), the majority having restricted systemic blood flow due to preductal coarctation (n = 15). The mean gestational age was 39.3 ± 1.7 weeks (range 33–43) and the mean birth weight was 3213 ± 613 g (range 1265–4300 g).

PGE_1 infusion was always started on the day of admission after the echocardiographic diagnosis. Patients with complete transposition and cyanotic heart disease due to ductus dependent pulmonary circulation were admitted considerably earlier (15 h [range 2–94] and 41 h [range 24–192] respectively) than patients with restricted systemic blood flow (117 h [range 24–504]). Balloon atrioseptostomy was performed in all but one patient with complete transposition with a time delay of 15 h (range 2–94) and in 8 patients of group 2. Heart rates, systolic and diastolic blood pressure were obtained hourly during the first 24–48 h of PGE_1 treatment and every 4 h afterwards if the clinical condition was stable. Measurements were performed more often in patients with haemodynamic instability. The blood pressure was measured oscillometrically with a Dinamap device (CRITIKON). Respiratory rates were recorded hourly and apnoeic episodes requiring and not requiring intubation and artificial ventilation were noted. Additionally, heart and respiratory rates were taken from ten patients with complete transposition, who were not treated with PGE_1 in the years 1984–1985, but only underwent balloon atrial septostomy. The data of this group were compared with the recent transposition group.

Rectal temperatures were measured every 3 h and considered to be elevated when above 38.0° C. All infants were cared for in incubators which made temperature regulation possible.

Treatment efficacy for patients with cyanotic heart disease was determined by the improvement of their capillary oxygen saturation (SO_2) and for patients with complete transposition also by the persistence of systemic left ventricular pressures. The improvement of lower body perfusion, especially femoral artery pulses and pressures, was used in the patient group with restricted systemic blood flow.

PGE_1 doses are given in micrograms per kilogram per minute. The duration of therapy with each dose as well as the total duration were recorded.

Normal values for neonatal heart and respiratory rates and blood pressure were taken from previous studies: the heart rates reported for the 2nd–7th day after birth were smoothed [3]. Respiratory rates were related to the infant's weight taken as a simple parameter of maturity [15]. Systolic and diastolic blood pressures of healthy neonates were obtained with the Dinamap system and given for infants below and above 36 h [13]. Hypotension was defined as a systolic pressure below 2 standard deviations (SD) of the normal mean present for more than 30 min.

All intercurrent medical events during the PGE_1 treatment were recorded without ascribing them directly as drug-related side-effects. The report concentrates mostly on measurable parameters and omits observations based on personal judgements (for example irritability and cutaneous vasodilation).

Antibiotic drugs were not given routinely during PGE_1 treatment. If they had been previously started, they were continued for a short period and then stopped.

Statistics

To specify the number of standard deviations any mean value differed from the mean normal value, the so-called Z value was calculated according to the following formula:

$$Z = \frac{\text{mean value} - \text{mean normal value}}{\text{standard deviation of mean value}}$$

The Z value is the number of standard deviations by which the patient's value deviates from the mean value of the respective value of normal persons of the same age. Paired and unpaired Student's t-tests were used, respectively, to analyse differences in the SO_2 values before and after PGE_1 infusion, PGE_1 doses for initial and maintenance treatment and to compare heart and respiratory rates of patients with complete transposition with and without PGE_1 treatment. Significance was always determined at the 5% level.

Results

Duration of PGE_1 treatment

The mean duration of PGE_1 treatment was 253 h, the median being 137 and the range 8–1809 h. Thirty-seven patients who were treated longer than 48 h showed no evidence of increasing PGE_1 side-effects. The patients with the longest treatment belonged to the group with ductus dependent pulmonary circulation, eight of them being treated for more than 4 weeks. The most important reason for this approach was to allow a gain in body weight in order to reduce the risk of cardiac surgery: for example, a girl of 1800 g with pulmonary atresia/ventricular septal defect weighed 3425 g after 11 weeks of PGE_1 treatment and subsequently underwent successful right ventricular outflow tract reconstruction.

Dosage of PGE_1 treatment

The mean initial PGE_1 doses were similarly low for the two groups of cyanotic CHD (0.016 ± 0.007 vs 0.017 ± 0.006 µg/kg/min for groups 1 and 2), but higher for the patients with restricted systemic blood flow (0.02 ± 0.01 µg/kg/min). These patients, who were started later on PGE_1 treatment, were given considerably higher maintenance doses (1: 0.013 ± 0.008, 2: 0.013 ± 0.006, 3: 0.02 ± 0.01 µg/kg/min; ($P < 0.05$ for 1 and 2 vs 3). With respect to dosage, three therapeutic situations were retrospectively determined: firstly (a) the initial dose could be low-

Table 2 Initial and maintenance prostaglandin E_1 doses

Cardiac diagnosis	(*n*)	Initial dose ± SD (μg/kg/min) [range]	Maintenance dose ± SD (μg/kg/min) [range]
Complete transposition	a (22)	0.020 ± 0.008 [0.010–0.035]	0.012 ± 0.005 [0.003–0.028]
	b (23)	0.014 ± 0.004 [0.003–0.020]	
	c (5)	0.011 ± 0.004 [0.004–0.016]	0.019 ± 0.00 [0.014–0.027]
CHD with ductus dependent pulmonary flow	a (10)	0.020 ± 0.008 [0.011–0.033]	0.009 ± 0.004 [0.003–0.018]
	b (10)	0.014 ± 0.004 [0.003–0.020]	
	c (3)	0.017 ± 0.002 [0.015–0.021]	0.024 ± 0.001 [0.022–0.025]
CHD with ductus dependent systemic flow	a (4)	0.033 ± 0.004 [0.030–0.040]	0.022 ± 0.007 [0.016–0.034]
	b (10)	0.017 ± 0.010 [0.005–0.037]	
	c (4)	0.017 ± 0.001 [0.015–0.018]	0.028 ± 0.006 [0.020–0.035]

[a] Initial dose ≥ 0.005 μg/kg per minute as compared with maintenance dose
[b] Initial dose essentially unchanged
[c] Initial dose ≤ 0.005 μg/kg per minute as compared with maintenance dose

ered by more than 0.005 μg/kg per minute with respect to the maintenance dose. This was done in 36 cases (40%). On average, the maintenance dose was 0.008 μg/kg per minute lower than the initial dose. Secondly (b) the initial dose remained essentially unchanged in 43 patients (47%); however, these were significantly lower than the initial doses of (a) and lie closer to the maintenance doses of the respective groups. Thirdly (c) the initial dose had to be increased more than 0.005 μg/kg per minute in 12 patients (13%) to improve the clinical situation. On average, the initial doses were increased by 0.01 μg/kg per minute. When comparing the three groups of cardiovascular malformations (Table 2), the relative frequency of the three therapeutic situations was very similar for the cyanotic groups. In contrast, among the 18 newborns with restricted systemic blood flow the initial dose could be lowered only four times (22%) and their maintenance dose was even higher than the initial doses of the cyanotic groups. The temporal percentage of using PGE_1 doses > 0.02 μg/kg per minute took only 5.3% of the total treatment time of 23656 h. In contrast, doses < 0.01 μg/kg per minute were given for 10101 h, i.e. 42.7% of the time (Fig. 1).

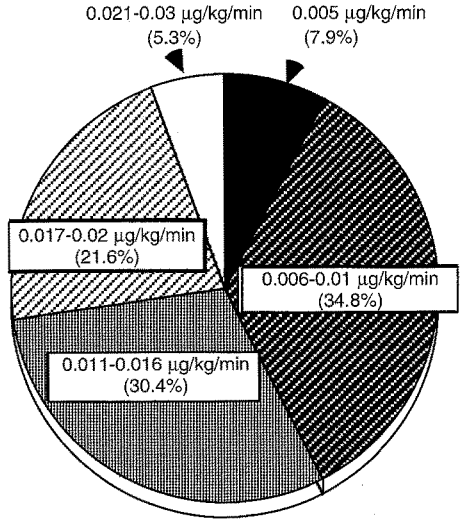

Fig. 1 Temporal percentages of different PGE_1 doses; total time of treatment: 23656 h

Efficacy of PGE_1 treatment

In the transposition group, PGE_1 infusion dramatically improved the systemic oxygen saturation from 50% ± 11% to 67% ± 8% ($P < 0.05$). Subsequent balloon atrial septostomy (BAS) resulted in a further increase to 72% ± 9% (Fig. 2a). The left to right ventricular pressure ratio at the time of catheterization was similar at the time of the arterial switch operation 11.8 ± 8.8 days later (Fig. 2b). However, three patients showed echocardiographic evidence of a left ventricular pressure drop, which could be reversed in two cases by increasing the PGE_1 dosage. In infants with ductus dependent pulmonary circulation, capillary oxygen saturation improved from 56% ± 10% to 69% ± 13% after PGE_1 infusion and subsequent BAS in eight of them ($P < 0.05$). All neonates with cardiac malformations leading to ductus dependent systemic circulation showed improvement in lower body perfusion, especially in femoral artery pulses and pressures.

Analysis of cardiovascular profile

Data of systolic and diastolic blood pressures of the three groups are given in Table 3. The differences in the systolic and diastolic blood pressures from the normal mean (Z values) are shown in Fig. 3. During the first 36 h after birth, newborns with complete transposition had slightly increased systolic (Z = 0.34 ± 0.93 SD) and diastolic (Z = 0.27 ± 0.9 SD) pressures. Afterwards, the systolic values were completely normal (Z = 0.01 ± 0.84 SD) and the diastolic values were lowered (Z = 0.24 ± 0.96 SD). Nineteen patients (38%) had periods of hypotension (i.e. systolic pressures > 2 SD below normal for more than 30 min) which were treated mostly by fluid replacement. The

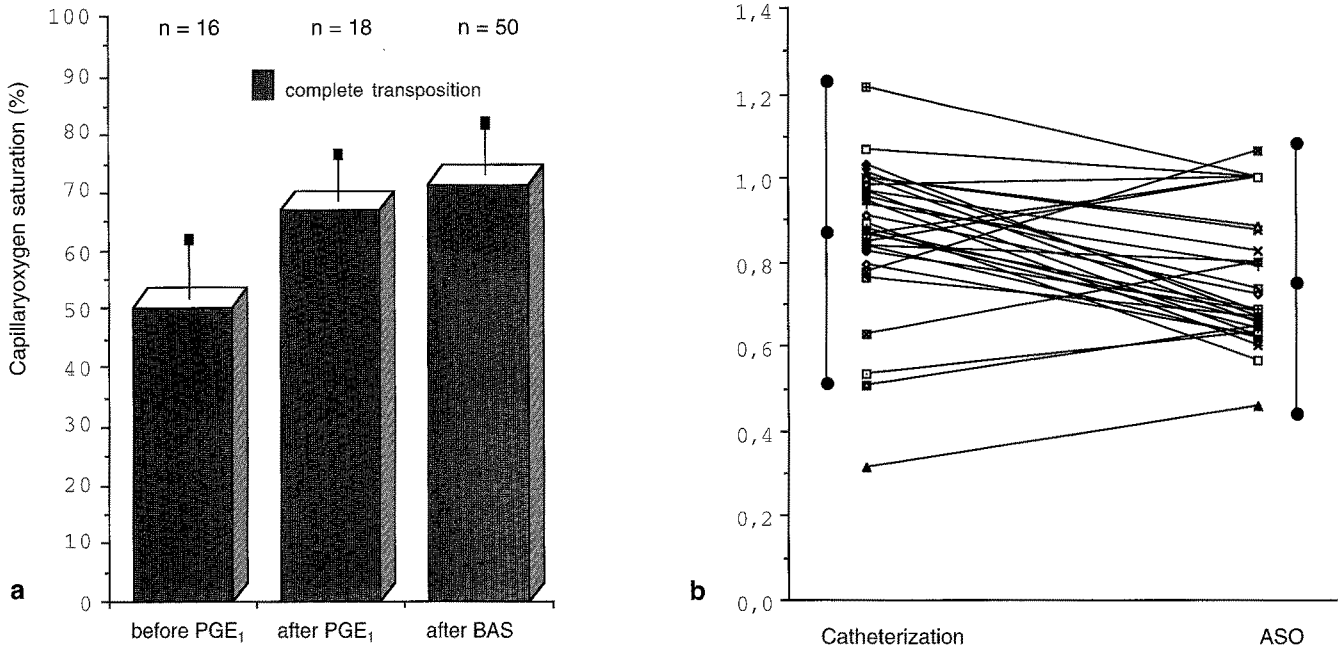

Fig. 2 **a** Capillary oxygen saturation of patients with complete transposition before and after PGE_1 infusion and after additional balloon atrial septostomy *(BAS)*. **b** Left to right ventricular pressure ratio at the time of catheterization and the arterial switch operation *(ASO)* 11.8 ± 8.8 days later

Table 3 Systolic and diastolic blood pressures of PGE_1 treated patients with cardiovascular malformations (for explanation of group numbers see Table 1)

Group	Age	Systolic pressure (mm Hg) [range]	Diastolic pressure (mm Hg) [range]
1	< 36 h	66 ± 7 [52–82]	44 ± 9 [32–69]
	> 36 h	68 ± 8 [52–104]	41 ± 5 [32–57]
2	< 36 h	58 ± 6 [44–63]	35 ± 4 [25–39]
	> 36 h	68 ± 7 [52–90]	41 ± 4 [32–50]
3	> 36 h	88 ± 19 [54–90]	56 ± 11 [37–50]

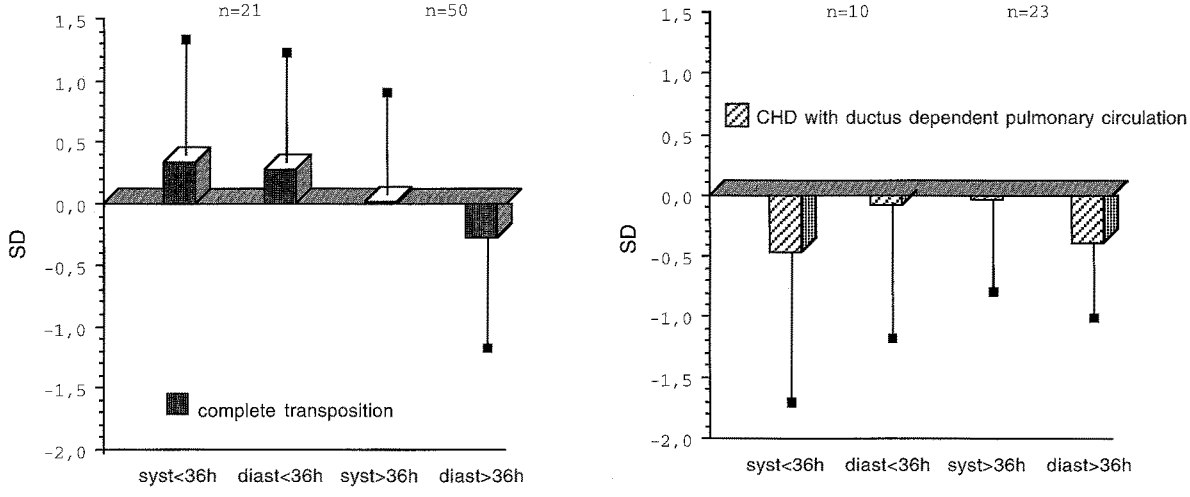

Fig. 3 Differences of systolic and diastolic blood pressures from normal mean (Z-values) in patients with complete transposition and CHD leading to obstructed pulmonary blood flow

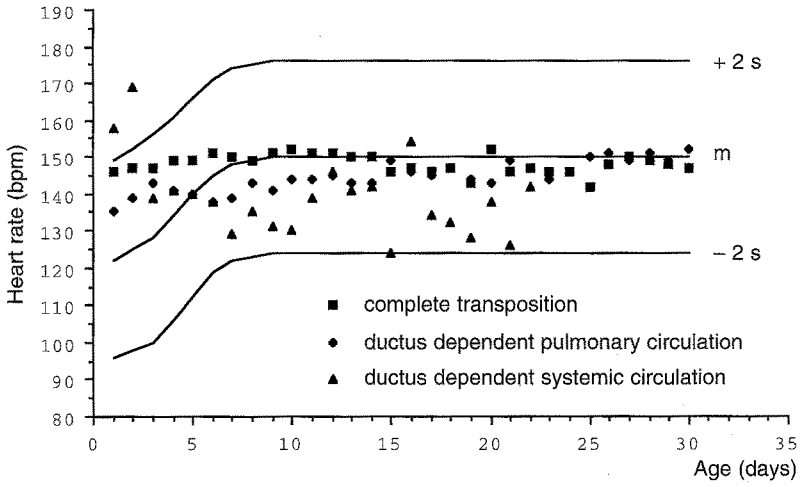

Fig. 4 Heart rates of patients with PGE_1 treatment (m ± 2 s according to [3])

systolic blood pressures of newborns with obstructed pulmonary blood flow were initially (< 36 h) 0.47 ± 0.69 SD below normal, thereafter the systolic values normalized, whereas the diastolic values were 0.38 ± 0.69 SD lower. Eight patients (35%) had periods of hypotension, which were also always easily managed. The upper limb systolic and diastolic blood pressures of patients with restricted systemic blood flow were considerably elevated (Z = +2.28 ± 2.25 and 1.89 ± 1.83 SD, respectively) despite improved circulation of the lower limbs.

The average heart rates were higher than normal in all groups of cardiovascular malformations during the 1st week of life (i.e. the early phase of PGE_1 treatment), but normalized afterwards (Fig. 4). When heart rates of patients of similar age and weight with complete transposition after BAS were compared with and without prostaglandin treatment, they were significantly higher in the PGE_1 treated group (149 ± 11 vs 129 ± 5/min).

Analysis of respiratory profile

Infants breathed spontaneously during 20417 (86.3%) of the 23656 h of PGE_1 treatment, but needed respiratory support for 3239 (13.7%) hours. Artificial ventilation had been started for treatment of hypoxaemia or shock in 47 (52%) newborns prior to knowledge of the underlying heart disease. Thirty-six cases remained intubated, as surgery was planned within a short time interval, while 11 cases on PGE_1 therapy were successfully weaned from the ventilator. Fourty-four patients never needed respiratory support before surgery. Thus, spontaneous respiration could be evaluated in 55 patients. The respiratory rate was significantly increased in all patient groups (Fig. 5). Compared to newborns with complete transposition not treated with PGE_1, the recent study group showed a significantly higher respiratory rate (63 ± 13 vs 48 ± 4/min).

Of 55 infants (38%) 21 developed apnoeas, 12 of them with complete transposition and 9 with ductus dependent pulmonary blood flow. In contrast, these never occurred in patients with ductus dependent systemic circulation. No recurrences of apnoeas occurred after lowering the dose in 16 cases, whereas 5 needed artificial ventilation. When comparing the number of spontaneously breathing patients who had apnoeas during PGE_1 treatment with doses < and > 0.01 µg/kg per minute, it was twofold with higher doses (n = 10 vs 5), while six suffered apnoeas within both dose ranges. Apnoeas were prevalent nearly twofold with higher than lower doses. Figure 6 relates the number of apnoeas at different dose levels to the respective treatment time. One apnoea occurred within 741 h of treatment with doses > 0.01 µg/kg per minute, compared to one per 500 h with lower doses. Within the range of weights (2250–4300 g) observed in this study, the incidence of apnoeas was not significantly increased among children with low weights.

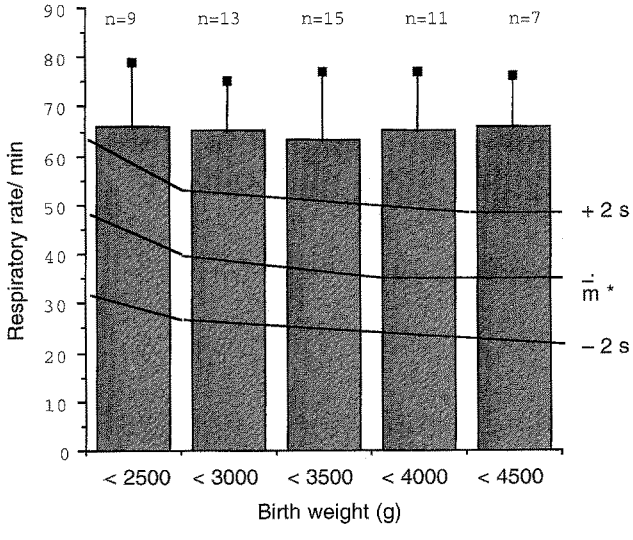

Fig. 5 Respiratory rates of 55 spontaneously breathing cardiac patients during PGE_1 treatment (m ± 2 s according to [14])

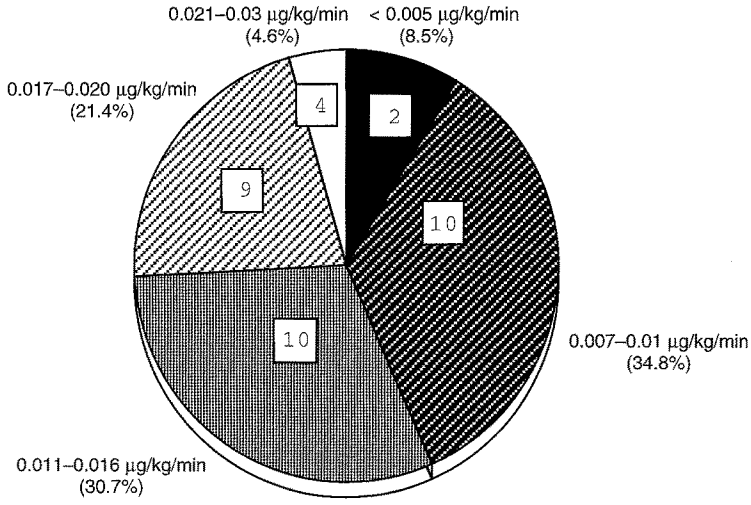

Fig. 6 Relation of apnoea prevalence (numbers in squares) to the respective treatment time with different PGE_1 doses (segments – % of total treatment time of 20417 h)

Other side-effects

During the course of treatment, 36 patients (39.6%) had temperatures exceeding 38.0° C up to three times. They could be lowered in most cases by lowering the incubator temperature.

Friability of the ductus arteriosus was regularly observed by our surgical colleagues. This had surgical implications once during an arterial switch operation, where bleeding from the ductal site necessitated an additional lateral thoracotomy. Two newborns developed severe necrotising enterocolitis which required laparotomy and colostomy, but both recovered. Occasional screening for blood in the faeces of asymptomatic patients often yielded positive results.

Discussion

This study proves effective PGE_1 treatment of ductus dependent CHD with lower doses than recommended by the manufacturer, especially for the initial treatment [20]. A dose of 0.1 µg/kg per minute was used in the original multicentre study and maintained in 59% of the patients throughout the entire infusion [11]. However, when analysing the experiences of their study the authors recommended to start treatment with 0.05 µg/kg per minute PGE_1 and reduce the dose to one half once stable improvement is achieved. Hallidie-Smith [7] used 0.1 µg/kg per minute in the first 6 patients, but afterwards reduced the doses stepwise to 0.01 µg/kg per minute and lower for the last 16 of the total 52 patients. While no failures with these lower PGE_1 doses were observed, the author recognized, however, the potential fallacies of small numbers and individual tolerance. We do not have sufficient experience with these low doses for use as initial treatment, but used them for more than 10,000 h as a maintenance dose. From our data, an initial dose of 0.015 µg/kg per minute is sufficient except in very few cases where higher doses may be required. This should be considered particularly in newborns beyond the 1st week of life who are admitted for cardiovascular malformations with restricted systemic flow. In these patients, who often develop clinical symptoms more slowly because of ductus constriction, higher doses for initial and maintenance treatment were necessary. Time delay between the progressive closure processes of the duct [6] and the start of PGE_1 treatment may explain a partial loss of ductal responsiveness to prostaglandins and the necessity for higher PGE_1 dosages. However, as a rule, we recommend initial doses of 0.015 µg/kg per minute PGE_1 and increase the dose only if the clinical condition improves inadequately. Our highest dose was 0.04 µg/kg per minute. We do not believe that higher doses are necessary for reopening a constricted ductus.

While most reports concentrate on the use of prostaglandins for malformations with restricted systemic or pulmonary blood flow [17, 19, 22], experience with their use in infants with complete transposition before and especially after BAS is more limited [1, 5]. These newborns showed a sharp rise of oxygenation after PGE_1 treatment before BAS was performed. Although BAS was done in 38% of our cases shortly after admission, this was no longer an emergency procedure. However, in cases with a restrictive interatrial communication backdamming of elevated left atrial pressure through the pulmonary venous circuit can occur and lead to pulmonary oedema and haemorhage [9]. This should be carefully considered when PGE_1 therapy is carried out without BAS, as an arterial switch operation is available within a short time interval.

The duration of PGE_1 treatment exceeded 1 week in 40% and 48 h in as many as 81% of our patients. Lewis et al. [11] reported an increased incidence of cardiovascular and central nervous complications in patients treated with PGE_1 for more than 48 h. However, this subgroup con-

sisted of only 62 (13.5%) of the total 460 cases. We did not find an increase in side-effects during long-term treatment, probably due to the much lower maintenance doses. While short-term treatment is the rule, a longer duration of treatment may be necessary to overcome other clinical problems prior to surgery, such as septicaemia or respiratory distress due to lung disease. In addition to the advantage of being able to elect the time of surgery, long-term treatment has considerable benefits for low birth weight infants. For selected cases, it provides an opportunity for gaining weight in order to reduce the risk of cardiac surgery, improve its quality or even allow a more favourable surgical approach, since corrective instead of palliative surgery can be performed [14, 19, 22].

Our study provides a more detailed investigation of the cardiovascular and respiratory profile of PGE_1 treated patients than found in earlier reports [5, 7, 8, 16]. The systolic blood pressures were no different from normal values, while the diastolic pressures were slightly lowered. This can be firstly explained as a result of opening of the duct and secondly of the PGE_1 mediated vasodilation. Periods of hypotension were observed in 38% of our cases, but were never serious and could always be easily treated by volume replacement. Despite the use of higher PGE_1 doses in the multicentre study [11], hypotension was reported for only 4% of the cases and was not mentioned in two other studies [7, 8]. The different values may not be comparable, as the criteria for hypotension (systolic pressure below 2 SD of normal mean) may have been different from ours, but were not presented.

The rather stable haemodynamic condition of our patients is emphasized by their normal heart rates. Compared to mean normal values, they were increased only during the 1st week of life, which however mostly coincides with the early phase of treatment. Schöber et al. [16] showed an acute fall in blood pressures and compensatory increase of heart rates after PGE_1 administration, which is followed by a new steady state. It may also be speculated that the physiologically high vagal tone of healthy newborns during this time period is not present in critically ill newborns.

The increased respiratory rate can firstly be related to the heart disease itself, but PGE_1 treatment may act as an additional haemodynamic burden by decreasing the pulmonary compliance due to volume load. This was shown by analysing the case reports of 10 infants with complete transposition, who underwent only BAS, but not PGE_1 treatment and had significantly lower respiratory rates.

Apnoeas are one of the most serious complications of PGE_1 therapy. Hallidie-Smith found respiratory depression to be dose dependent, with apnoeas occurring only with doses > 0.05 μg/kg per minute and hypoventilation > 0.03 μg/kg per minute [7]. Our patients, however, suffered apnoeas also with lower doses, the frequency being one per 500 h of treatment with doses < 0.01 μg/kg per minute and one per 741 h with higher doses. Although considerably higher PGE_1 doses were used in the multicentre study, the high number of apnoeas was similar [11]. However, our percentage includes only those patients breathing spontaneously, while in the multicentre study the number of patients with mechanically assisted ventilation before PGE_1 administration, thereby masking respiratory depression, was not known. In our experience, the low frequency of apnoeas with low PGE_1 doses makes respiratory support not a prerequisite for treatment, which is nicely demonstrated by the fact that we needed artificial respiration only for 13.7% of the total treatment time of 23656 h.

Elevated temperatures are of no concern when high doses for initial treatment are avoided. Hallidie-Smith [7] defined fever as temperatures > 37.2° C occurring more than once per 24 h which they observed in only 11 of 52 cases. Lewis et al. [11] listed elevated temperatures among the side-effects of the central nervous system, which also included seizure like activity and jitteriness.

Two of our 91 cases developed a necrotizing enterocolitis during PGE_1 treatment. A similar prevalence of this life-threatening complication was observed by others [7, 17], while a recent study reported a 20% occurrence among 34 low-dose treated patients with no need for abdominal surgery [18]. The pathogenesis is complex and multifactorial [12]. A relation to numerous agents and adverse events as perinatal asphyxia, umbilical catheters or cardiac catheterization has been reported [4, 21]. Leung et al. [10] identified hypotension and apnoea as the main causes of necrotizing enterocolitis in prostaglandin treated newborns with CHD. A recent Doppler study of newborns with patent ductus arteriosus found diastolic reversal of blood flow from the descending aorta into the pulmonary circulation [2]. In PGE_1 treated patients this disturbance of bowel perfusion is a specific consequence of drug-related duct patency and may contribute to the development of enterocolitis. Periods of severe hypotension would be an additional burden of perfusion and should be avoided by using low-dose treatment.

The overall incidence of PGE_1 side-effects is difficult to compare between studies, since different definitions were used. For example, tachycardia >180 bpm was considered to be a side-effect by one author [8], but not by others. Therefore, comparisons of studies are in this respect reliable only to a certain point. As the majority of PGE_1 side-effects is believed to be dose-dependent, it is astonishing, that Hallidie-Smith [7] observed 50% more side-effects than the multicentre study [11] in which much higher doses were used. On the other hand, we could not confirm a lack of side-effects with doses below 0.01 μg/kg per minute, which was reported by the same author [5].

In conclusion, PGE_1 can be successfully administered in less than the recommended doses. In particular, high initial doses can be avoided and low maintenance doses allow long-term treatment without serious complications.

References

1. Beitzke A, Suppan C (1983) Use of prostaglandin E_2 in management of transposition of great arteries before balloon atrial septostomy. Br Heart J 49: 341–344
2. Coombs RC, Morgan MEI, Durbin GM, Booth IW, McNeish AS (1990) Gut blood velocities in the newborn: effect of patent ductus arteriosus and parenteral indomethacin. Arch Dis Child 65: 1067–1071
3. Davignon A, Rautaharju P, Boiselle E, Soumis F, Megelas M, Choquette A (1981) Normal ECG standards for infants and children. Pediatr Cardiol 1: 123–131
4. Dickinson D, Galloway R, Wilkinson J, Arnold R (1982) Necrotising enterocolitis after neonatal cardiac catheterisation. Arch Dis Child 57: 431–433
5. Freed M, Heymann M, Lewis A, Roehl S, Kensey R (1981) Prostaglandin E_1 in infants with ductus arteriosus dependent congenital heart disease. Circulation 64: 899–905
6. Gittenberger-de-Groot A, Strengers J (1988) Histopathology of the arterial duct (ductus arteriosus) with and without treatment with prostaglandin E_1. Int J Cardiol 19: 153–166
7. Hallidie-Smith K (1984) Prostaglandin E_1 in suspected ductus dependent cardiac malformation. Arch Dis Child 59: 1020–1026
8. Host A, Halken S, Kamper J, Lillquist K (1988) Prostaglandin E_1 treatment in ductus dependent congenital cardiac malformation. Dan Med Bull 35: 81–84
9. Kachaner J (1992) Role of prostaglandin infusion prior to surgery in complete TGA. In: Vogel M, Bühlmeyer K (eds) TGA 25 years after Rashkind balloon septostomy. Steinkopff Verlag, Darmstadt, pp 73–78
10. Leung MP, Chau K, Hui P, Tam A, Chan F, Lai C, Yeung C (1988) Necrotising enterocolitis in neonates with symptomatic congenital heart disease. J Pediatr 113: 1044–1066
11. Lewis A, Freed M, Heymann M, Roehl S, Kensey R (1981) Side effects of therapy with prostaglandin E_1 in infants with critical congenital heart disease. Circulation 64: 893–898
12. MacKendrick W, Caplan M (1993) Necrotizing enterocolitis. New thoughts about pathogenesis and potential treatments. Pediatr Clin N Am 40: 1047–1059
13. Park M, Lee D (1989) Normative arm and calf blood pressure values in the newborn. Pediatrics 83: 240–243
14. Pitlick P, French J, Maze A, Kimble K, Ariagno R, Reitz B (1980) Long-term low-dose prostaglandin E_1 administration. J Pediatr 96: 318–320
15. Schmalisch G, Wauer R (1987) Perzentilkurven zur Interpretation atemmechanischer Parameter von Neugeborenen. Kinderärztl Praxis 55: 587–594
16. Schöber J, Kellner M, Mocellin R, Schumacher G, Bühlmeyer K (1980) Indications and pharmacological effects of therapy with prostaglandin E_1 in the newborn. Adv Prostaglandin Thromboxane Res 7: 415–421
17. Silove E, Roberts D, De Giovanni J (1985) Evaluation of oral and low dose intravenous E_2 in management of ductus dependent congenital heart disease. Arch Dis Child 60: 1025–1030
18. Singh GK, Fong LV, Salmom AP, Keeton BR (1994) Study of low dosage prostaglandin – usages and complications. Eur Heart J 15: 377–381
19. Teixeira O, Carpenter B, MacMurray S, Vlad P (1984) Long-term prostaglandin E_1 therapy in congenital heart defects. J Am Coll Cardiol 3: 838–843
20. Upjohn-Company (1988) Pediatric alprostadil package insert. Kalamazoo, Michigan
21. Wiswell T, Robertson C, Jones T, Tuttle C (1988) Necrotizing enterocolitis in full-term infants. Am J Dis Child 142: 532–535
22. Yokota M, Muraoka R, Aoshima M, Nomoto S, Shiraishi Y, Kyoku I, Kitano M, Shimada I, Nakano H, Ueda K, Saito A (1985) Modified Blalock-Taussig shunt following long term administration of prostaglandin E_1 for ductus-dependent neonates with cyanotic congenital heart disease. J Thorac Cardiovasc Surg 90: 399–403